

Heart failure with preserved ejection fraction

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Diastolic heart failure is a disorder characterized by impaired left ventricular (LV) relaxation and increased LV stiffness. Heart failure with preserved ejection fraction (HFPEF) accounts for 40% to 50% of all HF cases and has a prognosis that is as dangerous as that of systolic HF.^{1,2} Nowadays, HF is growing into a major health problem, so that recent HF guidelines have placed special emphasis on the detection of LV systolic and diastolic dysfunction and the timely identification of risk factors for HF.¹ Therefore, the issue addressed in the article of Brzyżkiewicz et al¹ is particularly important. The authors aimed to evaluate the prevalence of HF diagnosis in hypertensive patients with the first stage of diastolic dysfunction, namely, impaired relaxation. They based the diagnosis of HFPEF on the 2012 European Society of Cardiology (ESC) guidelines,² which require 4 conditions to be fulfilled: 1) typical symptoms of HF; 2) typical signs of HF; 3) normal or only mildly reduced LV ejection fraction (LVEF) without LV dilation; and 4) relevant structural heart disease (LV hypertrophy/left atrial enlargement) and/or diastolic dysfunction.² This definition seems to be relatively precise; however, each of the listed conditions requires special attention.

The experienced clinicians are aware that “typical symptoms of HF” are not so obvious and may be considered as specific for HF only as a symptom complex, supported by the results of additional tests. Most of the HF symptoms taken separately are nondiscriminating and of limited diagnostic value.^{3,4} Typical signs of HF may not be present in the early stages of HF and may be masked by using diuretics in the therapy. There are numerous trials that used different cut-off points for the diagnosis of the third condition, that is, normal or only mildly reduced LVEF. However, the majority of investigators agree that LVEF exceeding 50% is “normal” and LVEF below 30% to 35% is “reduced”. The question remains as to how to classify patients with LVEF between 35% and 50% (the so called grey area). Given the fact that in more than 30% of patients in a 2-dimensional echocardiographic examination (commonly used for LVEF assessment), the clear definition

of the endocardium without the use of intravenous contrast is lacking,⁵ the cut-off value of 50% for LVEF to dichotomize HFPEF from HF with reduced ejection fraction (HFREF) is somewhat arbitrary. Maybe the simultaneous use of 2 methods, namely, echocardiography, which is more precise for LV diastolic dysfunction assessment, and cardiac magnetic resonance (CMR), which is better for systolic dysfunction evaluation, is the optimal solution, as proposed by Leong et al.⁶ What is established for now, the characterization of HF patients should be as wide as possible, including (except for certain clinical examinations) additional tests described by Brzyżkiewicz et al¹ such as echocardiography, chest X-ray, and laboratory tests with special attention to HF-specific natriuretic peptides. A wide spectrum of diagnostic tests not only dedicated to HF is especially important in patients with HFPEF, where differential diagnosis is pivotal.

The above considerations lead to a conclusion that diagnosis and, in consequence, the real prevalence of HFPEF are not so easy to establish. The estimate indicates that the prevalence of HFPEF among patients with HF might be about 54%, ranging from 40% to 71%,⁷ which is in agreement with the results of one of the largest trials, the Copenhagen Hospital Heart Failure Study, in which the prevalence of HFPEF was 61%.⁸ Data from the National Health and Nutrition Examination Survey (NHANES) suggest an increase of 46% in the prevalence of HFPEF by 2030.⁹ In clinical practice, an echocardiographic examination is crucial for the determination of the fourth condition in HFPEF, namely, “relevant structural heart disease (LV hypertrophy/left atrial enlargement) and/or diastolic dysfunction”.²

The recommendations of American and European echocardiography societies¹⁰ as well as the ESC guidelines for the diagnosis and treatment of acute and chronic HF² agree that a good definition of LV diastolic dysfunction needs to evaluate more than 1 group of indices. The echocardiographic techniques to assess LV systolic and diastolic function have evolved rapidly over the past years. New techniques of tissue Doppler

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imaging (TDI) enable the measurement of myocardial velocities and provide valuable information about LV diastolic function in addition to classical echocardiography and pulsed-wave Doppler ultrasound. Currently, the absolute minimum is to assess the LV regional lengthening velocity (e') from TDI and parameters of mitral inflow. The left atrial volume index (LAVI) and the above parameters are used to precisely grade LV diastolic dysfunction into 3 grades. Echocardiographic parameters, especially those used for assessing LV relaxation and filling pressure, depend not only on volume load but also on age, heart rate, and body size. The gold standard for assessing diastolic function remains the pressure–volume relationship, but this requires an invasive approach. Therefore, a comprehensive assessment of a number of echocardiographic variables is required to evaluate diastolic function as correctly as possible, and even so, the relationship between echocardiographic and invasive hemodynamic parameters remains modest.¹¹

Although not widely recommended, the new possibilities for the early detection of LV diastolic dysfunction are provided by echocardiography: diastolic stress testing, speckle tracking-based early diastolic longitudinal strain rate, and speckle tracking-based circumferential strain measurements. In this area, CMR offers the analysis of LV volume changes over time, which can be converted to filling curves as well as direct blood flow velocity measurement by velocity encoding or “phase-contrast” CMR. Using gated CMR, transmitral and pulmonary vein flow can be measured similarly to echocardiographic Doppler values. The most recent, not yet validated, ability of the CMR technique is the measurement of tissue velocity (LV walls).¹²

The study group in the discussed paper consisted mainly of patients with arterial hypertension and diabetes mellitus who seem to be the most relevant choice for identifying LV diastolic dysfunction especially in early phase, that is, isolated abnormalities of LV relaxation. The recent 2013 European Society of Hypertension / ESC guidelines for the management of arterial hypertension include only LV hypertrophy to the organ damage signs influencing prognosis in hypertensive subjects. Nevertheless, the guidelines underscore that the most typical hypertension-induced diastolic dysfunction is associated with concentric geometry and can induce symptoms/signs of HF itself, even when LVEF is still normal.¹³ Thus, the guidelines recommended the measurement of 3 echocardiographic diastolic dysfunction parameters: LAVI, septal and lateral e' velocity, and E/e' -filling pressure index. The prognostic value of all these indices has been recognized in hypertensive subjects. An increased E/e' ratio is associated with increased cardiovascular risk independently of LV hypertrophy.¹⁴ The LAVI exceeding the cut-off point of 34 ml/m² is an independent predictor of atrial fibrillation, ischemic stroke, and fatal cardiovascular events. In hypertension, LV relaxation

abnormalities are the consequence of hemodynamic abnormalities, while in diabetes—rather of metabolic disturbances.¹⁵ The cumulative deteriorating effect of those 2 conditions was well documented in the study by Brzyżkiewicz et al.¹ A relatively high prevalence (42%) of HFPEF among patients with isolated LV relaxation abnormalities (early and mild phase of diastolic dysfunction) in this study should not be surprising because all patients were hypertensive, more than half of them were diabetic, female, and rather old than young, judging from the mean age of 59 years.

Age, female sex, arterial hypertension, diabetes, atrial fibrillation, and LV structural abnormalities are the well-documented risk factors for HFPEF.² The results of the discussed study are in agreement with previously reported data, which emphasized the importance of hypertension, diabetes, age, kidney disease, and LV functional abnormalities as predictors of HFPEF. In a recently published exploratory study of patients enrolled in the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE), a statistical approach was used to identify HFPEF subgroups and validated using the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved study, which may potentially differ in prognosis.¹⁶ Clinical profiles and prognosis of the 6 predefined subgroups were similar in the CHARM-Preserved study. The 2 subgroups with the worst event-free survival in both studies were characterized by a high prevalence of obesity, hyperlipidemia, diabetes mellitus, anemia, or renal insufficiency and by female predominance, advanced age, lower body mass index, high rates of atrial fibrillation, valvular disease, renal insufficiency, or anemia, respectively.¹⁶ These data, together with the findings of Brzyżkiewicz et al.,² highlight the need for active searching for the signs and symptoms of HF in patients with certain clinical characteristics and confirmation in further laboratory tests and imaging evaluation. The diagnosis of HFPEF provides information on poor prognosis; however, no treatment has yet been shown to convincingly reduce morbidity and mortality in patients with diastolic HF.^{2,16} That it is why, an adequate treatment of hypertension and myocardial ischemia is considered to be important, as is control of the ventricular rate in patients with atrial fibrillation.² The necessity of proper treatment of obesity, diabetes, and hyperlipidemia should be also kept in mind.

In conclusion, the study by Brzyżkiewicz et al.¹ suggests that the “known unknowns” of HFPEF should be more widely explored to appropriately evaluate its prevalence and prognosis and to facilitate the development of a life-protecting treatment.

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